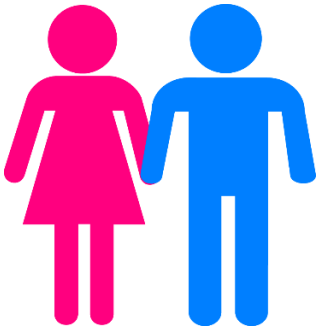
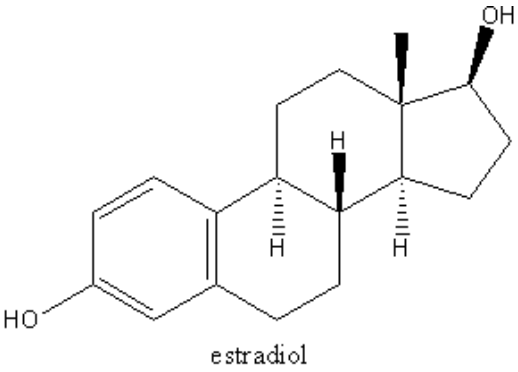


Sex as a biological variable: Considering female hormones' effects on dopamine signaling could offer new therapeutic insights

Many psychiatric and neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, schizophrenia, depression, ADHD, and drug addiction are known to exhibit considerable sex differences in terms of onset, prevalence, severity, and treatment outcomes (Loke et al., 2015; Rubin et al., 2015). However, our understanding of mechanistic neurobiological differences between males and females is limited (but see Gillies & McArthur, 2010). In response to this, the National Institutes of Health has recently taken steps to emphasize the importance of sex as a biological variable (also see). Preclinical research using animal models has rarely dealt with the complexity of studying females as multiple measurements would have to be taken across their naturally fluctuating estrus (rodents) and menstrual cycles (primates) to categorize the effects of sex hormones on measures of interest. Researchers complain that such approaches are, admittedly, more time consuming and expensive to conduct. However, growing research indicates that sex and sex hormones can have effects on biological function. Until we better understand these effects, we can't hope to develop treatments that are equally efficacious in both men and women.



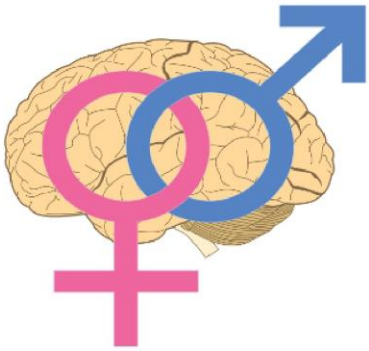
estradiol

As a researcher interested in studying the role of dopamine in human behavior, the female hormone estradiol is particularly interesting to study as it has been shown to increase striatal dopamine synthesis (Pasqualini et al., 1995) and levels of tyrosine hydroxylase, the rate limiting enzyme in the dopamine biosynthetic pathway (Ivanova & Beyer, 2003). Furthermore, estradiol increases dopamine D2 receptor density, both when administered exogenously and during endogenous estrous cycle fluctuations in rodents (Bazzett & Becker, 1994; Di Paolo et al., 1988) and monkeys (Czoty et al., 2009).

Drug-seeking behavior has also been correlated with estradiol fluctuations throughout the menstrual cycle (Becker & Hu, 2008; Roberts et al., 1989) and estradiol administration to ovariectomized rats increases drug-seeking behavior and self-administration rates of cocaine (Jackson et al., 2006). Furthermore, estradiol has been associated with increased dopamine release in response to the psychostimulant d-amphetamine (dAMPH) in rats (Becker, 1990; Becker, 1999) and, along with progesterone, differential subjective responses to dAMPH in humans (Justice et al.,

2002). Thus, there is strong evidence that female hormones can modulate the pleasurable effects of drugs of abuse in the brain. Indeed, stress and cue-induced craving for cocaine varies across the menstrual cycle (Sinha et al., 2007; and see review).

Estradiol goes beyond just acting on affective systems to induce feelings of pleasure and



can modulate cognitive processes that are often compromised in individuals with drug abuse disorders. For instance, estradiol has been shown to affect effort-based decision making in rats (Uban et al., 2012) and working memory (Jacobs & D'Esposito, 2011) and temporal discounting choices in human subjects (Smith et al., 2014), dependent on putative levels of prefrontal cortical dopamine. These data suggest that estradiol affects dopamine-related processes across the brain from deep limbic/motivational structures to higher order cortical areas.

While the preclinical data mentioned above suggests that female hormones should affect dopamine signaling in human subjects, definitive demonstration of estradiol's involvement in human dopamine signaling at the neuroanatomical level is currently lacking. However, human PET studies have demonstrated differences across males and females in dopamine release (Munro et al., 2006; Riccardi et al., 2006), dopamine synthesis capacity (Laakso et al., 2002), and dopamine D2 receptor availability (Kaasinen et al., 2001). Beyond one study limited in sample size (n=5) and only imaging D2 receptors in the striatum (Nordstrom et al., 1998), we lack data on measures of human dopamine signaling across the menstrual cycle.

Thus, future human PET studies of the dopamine system should begin to investigate the role of female hormones in their measures, whether they be dopamine synthesis, dopamine receptor/transporter levels, or dopamine release. Even just collecting blood on PET scan days to later quantify plasma hormone levels could be useful. Due to the expense of PET imaging, undoubtedly data will have to be compiled across multiple studies and sites to have the necessary power to explore female hormone - dopamine relationships. This work is important, though, as understanding the particulars of how these hormones modulate the dopaminergic system could offer insights into therapies to modulate the dopamine system in individuals (male or female) with substance use disorders or other psychiatric conditions associated with aberrant dopamine signaling.

For further reading:

Cosgrove et al., 2007

Barth et al., 2015

Toffoletto et al., 2014

Becker et al., 2012